REMARKS

Claims 1-68 are pending in the instant application. Claims 1-53 and 59-68 have been withdrawn from consideration. Claims 54 and 56 have been amended. Support for this amendment can be found at, *inter alia*, page 30, line 19 to page 31, line 16. Claim 55 has been amended. Support for this amendment can be found at, *inter alia*, page 4, lines 6-19. Claims 54, 56, and 57, have been amended to recite in a final step what the preamble set as a goal of the claimed method. Claim 58 has been amended. Support for this amendment can be found at, *inter alia*, page 20, lines 3-17. New claims 69 and 70 have been added. Support for the new claims 69 and 70 can be found in the specification as originally filed at, *e.g.*, p. 80, *ll.* 10-15. No new matter has been introduced. Claims 1-70 will be pending upon entry of the present amendment.

Page 6 of the specification has been amended to insert the appropriate SEQ ID NO and to correct minor typographical errors. Support for this amendment can be found in the specification at, *inter alia*, page 4, lines 20-29; page 4, line 33 to page 5, line 1; page 7, line 25 to page 8, line 4; page 40, lines 3-7; page 47, lines 18-21 and page 48, lines 4-5; and page 90, lines 4-10.

Pages 15, 118 and 112 of the specification have been amended to correct certain minor editorial errors. Specifically, pages 15 and 122 of the specification have been amended to correct minor typographical errors. Page 118 of the specification has been amended to clarify the description of the Example 13.

Page 19 of the specification has been amended to correct a typographical error. Support for this amendment can be found in the specification at, *inter alia*, page 4, lines 6-19.

Page 21 of the specification has been amended to clarify the description of the invention. Support for this amendment can be found in the specification at, *inter alia*, page 2, lines 15-20; page 11, lines 20-24; page 20, line 18 to page 21, line 6; page 21, lines 7-23; page 24, line 23 to page 25, line 31; page 82, lines 7-23; page 87, lines 9-14; Examples 3-6; and Examples 8-13.

Pages 48 and 49 of the specification have been amended to correct for typographical errors in the amino acids at positions 148 and 160. Support for this amendment can be found at page 47, lines 11-22; page 90, lines 4-10, and SEQ ID NO:10. Furthermore, one of skill in the art having knowledge of the published native sequence of erythropoietin (see Exhibit A) would know that the native amino acids at positions 148 and 160 are F (phenylalanine) and A (alanine), respectively, not P (proline) and C (cysteine).

Page 90 of the specification has been amended to clarify the difference in positions of amino acids in the full length (native) amino acid sequence and the mature amino acid sequence of erythropoietin. Support for this amendment can be found in Exhibit A. One of skill in the art having knowledge of the published full length (native) sequence of erythropoietin would know that the leader sequence is 27 amino acids. *See also* page 90, line 10.

No new matter has been introduced. Applicants respectfully request entry of the present amendments.

I. THE CLAIM OBJECTION TO CLAIMS 56-58, FOR INFORMALITIES, SHOULD BE WITHDRAWN

Claims 56-58 are objected to because they recite non-elected subject matter. These claims are generic (Office Action mailed 6/20/06; p. 5; ¶3). Upon allowance of a generic claim, Applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 C.F.R. § 1.141. Thus, the objection against claims 56-58 should be withdrawn.

The Examiner has further objected to claims 56-57 because they recite dependencies from non-elected claims 1-6. Upon allowance of claim 56 and/or 57, Applicants will re-write these claims as independent claims.

II. THE CLAIM OBJECTIONS FOR OBVIOUSNESS-TYPE DOUBLE PATENTING SHOULD BE HELD IN ABEYANCE

Claim 57 is rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-10 of U.S. Patent No. 6,531,121 B2.

Claims 54-58 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 35 and 37-38 of copending Application No. 10/188,905.

Claims 57-58 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and 15 of copending Application No. 09/716,960.

Claims 54-56 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 2 and 5 of copending Application No. 10/351,640.

Claim 57 is provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1 of copending Application No. 10/185,841.

Claim 57 is provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and 4 of copending Application No. 10/573,905.

In response, and without agreeing with the double patenting rejections, Applicants request the double patenting rejections be held in abeyance until indication of allowable subject matter in the present application.

III. THE CLAIM REJECTIONS UNDER 35 U.S.C. § 112, FIRST PARAGRAPH, ENABLEMENT, SHOULD BE WITHDRAWN

Claims 54-58 have been rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. In particular, the Examiner contends that the specification does not reasonably provide enablement for a method for protecting, maintaining or enhancing the viability of *any* cell, tissue, or organ isolated from a mammalian body comprising exposing said cell, tissue or organ to a pharmaceutical composition comprising *any* mutein recombinant tissue protective cytokine as broadly claimed, or a method for protecting against *any* tissue injury as broad claimed; prevention of tissue injury; restoring tissue and tissue function in a mammal; or rejuvenating tissue and tissue function in mammal comprising administering *any* mutein recombinant tissue protective cytokine as broadly claimed. As discussed in detail below, Applicants disagree with the Examiner's contentions that the full scope of the claims is not enabled.

A. The Legal Standard

The test for enablement is whether one reasonably skilled in the pertinent art could make or use the invention, without undue experimentation, from the disclosure in the patent specification coupled with information known in the art at the time the patent application was filed. *U.S. v. Telectronics Inc.*, 857 F.2d 778, 8 USPQ2d 1217 (Fed. Cir. 1988). In fact, well-known subject matter is preferably omitted. See *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384 (Fed. Cir. 1986) ("a patent need not teach, and preferably omits, what is well known in the art."). See *Northern Telecom, Inc. v. Datapoint Corp.*, 908 F.2d 931, 941 (Fed. Cir. 1990). These enablement rules preclude the need for the patent applicant to "set forth every minute detail regarding the invention." *Phillips*

Petroleum Co. v. United States Steel Corp., 673 F. Supp. 1278, 1291 (D. Del. 1991); see also *DeGeorge v. Bernier*, 768 F.2d 1318, 1323 (Fed. Cir. 1985).

Undue experimentation is experimentation that would require a level of ingenuity beyond what is expected from one of ordinary skill in the field. *Fields v. Conover*, 170 USPQ 276, 279 (CCPA 1971). The factors that can be considered in determining whether an amount of experimentation is undue have been listed in *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Among these factors are: the amount of effort involved, the guidance provided by the specification, the presence of working examples, the amount of pertinent literature and the level of skill in the art. The test for undue experimentation is not merely quantitative, since a considerable amount of experimentation is permissible, so long as it is merely routine. *Id.*

Further, while the predictability of the art can be considered in determining whether an amount of experimentation is undue, mere unpredictability of the result of an experiment is not a consideration. Indeed, the Court of Custom and Patent Appeals specifically cautioned that the unpredictability of the result of an experiment is not a basis to conclude that the amount of experimentation is undue:

> [If to fulfill the requirements of 112, first paragraph, an applicant's] disclosure must provide guidance which will enable one skilled in the art to determine, with reasonable certainty before performing the reaction whether the claimed product will be obtained, ... then all "experimentation" is "undue" since the term "experimentation" implies that the success of the particular activity is uncertain. Such a proposition is contrary to the basic policy of the Patent Act.
>
> *In re Angstadt*, 190 USPQ 214 (CCPA 1976), at 219.

Thus, all that is required is a reasonable amount of guidance with respect to the direction of the experimentation; reasonable certainty with regard to the outcome of the experimentation is not required.

In a more recent decision of the Board of Patent Appeals and Interferences ("Board"), the Board applied the principles of *Angstadt* to a biotechnological context. *In re Neuberger & Rabbitts*, 2002 WL 33952578 (B.P.A.I. 2002). The rejected claims in *Neuberger* were directed to chimeric antibodies with (i) certain antigen binding activity; and (ii) a certain biological activity. The Examiner in *Neuberger* had rejected these claims based on lack of predictability. The Board reversed the Examiner's decision because "a requirement for

certainty would be incompatible with any amount of experimentation and therefore incompatible with the standard of enablement." *Id.* at 3.

In addition, the Patent and Trademark Office bears the initial burden of establishing a *prima facie* case of non-enablement. *In re Marzocchi*, 169 USPQ 367, 369 (C.C.P.A. 1971); M.P.E.P. § 2164.02. A patent applicant's specification which contains a teaching of how to make and use the invention must be taken as enabling unless there is reason to doubt the objective truth of the teachings which must be relied on for enabling support. *Id.*

B. Claims 54-58 Are Enabled by the Instant Specification

The Examiner asserts that "[w]hile the skill level in the art is high, the level of predictability is low" (Office Action mailed 12/07/2006 at p. 10. l. 15) in support of her contention that "[t]he instant specification ... does not provide sufficient guidance or evidence that the claimed method can restore tissue lost to injury or regenerate new tissue or function" (*Id.* at p. 10, l. 22 to p. 11, l. 2). According to *In re Angstadt*, however, "the unpredictability of the result of an experiment is not a basis to conclude that the amount of experimentation is undue" 190 USPQ 214 (CCPA 1976), at 218-219. See also *Neuberger*.

1. No undue experimentation is required to make and use the claimed invention for *any* cell, tissue, or organ (claims 54-56)

The Examiner contends that the instant specification is not enabling for *any* cell, tissue, or organ. Specifically, the Examiner states that "as not all cells, tissues, organs possess EPO receptors and thus would not be considered 'erythropoietin responsive,' it is unclear how such cells and tissues would be protected, maintained or enhanced viably, etc. by the tissue protective cytokine." (Office Action, p. 12, ll. 15-18).

In an effort to expedite prosecution of the instant matter, Applicants have amended the language of claims 54 and 56. Specifically, claims 54 and 56 have been amended to recite "[a] method for protecting, maintaining or enhancing the viability of a responsive cell, a tissue comprising a responsive cell, or an organ comprising a responsive cell . . . ." Applicants direct the Examiner's attention to page 30, line 19 to page 31, line 16 of the instant specification for an explanation of the claim term "responsive cell." Accordingly, only cells that do respond to the tissue-protective activity of an EPO, and tissues or organs comprising such cells, are covered by the claims.

Numerous examples of such responsive cells, tissue comprising a responsive cell, or an organ comprising a responsive cell can be found on page 2, line 29 – page 3, line 20 and page 30, line 19 to page 31, line 16 of the instant specification.

The responsiveness of a given cell to an EPO can be tested without undue experimentation. Assays to test the responsiveness of a given cell to an EPO are provided in the specification, *e.g.*, at page 63, lines 12-16; and sections 6.6 to 6.12, beginning at page 111. The skilled artisan could adopt these assays for different types of cells, tissues, or organs without undue experimentation.

Thus, Applicants respectfully submit that in view of the amendment to the claims and the numerous examples of responsive cells, the specification enables one of ordinary skill in the art to make and use the full scope of the invention without having to engage in undue experimentation.

2. No undue experimentation is required to make and use claimed invention for *any* injury (claims 57-58)

The specification provides numerous detailed examples of assays that one of skill in the art could use to test a particular recombinant EPO for its ability to protect, maintain or enhance the viability of a cell, tissue or organ, or to protect against and prevent a tissue injury as well as to restore and to rejuvenate tissue and tissue function. While the outcome of a particular assay may not be known *ex ante*, this is not a grounds for concluding that the experimentation is undue because performing the assay requires merely routine experimentation.

For example, the specification describes in detail the Morris Water Maze Test (Example 10, pages 114-115), an assay used to demonstrate the ability of tissue protective cytokines to restore diminished cognitive function in mice after receiving brain trauma. Further working examples of assays for numerous types of injured tissue include injured tissue resulting from cardiac ischemia (Example 8, p. 113), retinal ischemia (Example 9, p. 114; Example 18, pp. 128-129), brain injury (Example 10, pp. 114-115) and spinal cord (Example 12, pp. 115-118) and allergic encephalomyelitis (Example 13, pp. 120-121).

The skilled artisan can follow the guidance provided in these examples to test the effectiveness of a tissue protective cytokine in other tissues, or for other tissue injuries.

There is nothing undue about the performance of these assays as they are merely routine tests.

The Examiner contends that the instant specification fails to provide any evidence or sound scientific reasoning to support a conclusion that the working examples could be extrapolated to methods of treating any injury. Applicants disagree.

Applicants further invite the Examiner's attention to the following study published subsequent to the filing date of the of the instant application which demonstrate that the claimed methods are also enabled for stroke:

(1) Villa, P. *et al.*, 2007, *Journal of Cerebral Blood Flow & Metabolism* 27, 552-563 ("Villa")(Exhibit B)

Villa analyzed the effects of nonerythropoietic forms of erythropoietin on the neurologic deficits of rats using the limb placing and foot-fault tests. The limb placing test evaluates sensorimotor integration in limb placing responses to visual, vibrissae, tactile, and proprioceptive stimuli. These neurological deficits are a measure for the extent of the underlying neurological injury. The foot-fault test measures the ability of the animal to integrate motor responses. Specifically, Villa tested the ability of EPO-S100E[1] and other forms of erythropoietin to improve neurological function after stroke. Villa found that EPO-S100E administered three hours after ischemia significantly improved the sensorimotor score in the limb-placing test at 1 and 14 days postoperatively, and reduced foot-faults compared with vehicle treatment at 7 and 14 days after stroke (see Fig. 7). Thus, these results demonstrate to one of ordinary skill in the art that mutein EPO protects against and prevents tissue injury as well as restores and rejuvenates tissue and tissue function in a mammal resulting from a stroke.

The case law is well-settled that not every species encompassed by the claims needs to be exemplified in the specification, as long as the disclosure teaches how to make and how to use the invention as broadly as it is claimed:

> [T]here must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and how to use the invention as broadly as it is claimed. This means that the disclosure must adequately guide the art worker to determine, without undue experimentation,

[1] EPO S100E is disclosed in the present specification as SEQ ID No. 62.

which species among all those encompassed by the claimed genus possess the disclosed utility.

In re Vaeck, 947 F.2d 488, 496 (Fed. Cir. 1991) (citing *In re Angstadt*, 537 F.2d 498, 502-03 (CCPA 1976).

As discussed above, the specification provides detailed disclosure regarding how to determine which conditions causing tissue injury are encompassed by claims 57-58. Additionally, the specification provides working examples, *i.e.*, Examples 8-10, 12, 13 and 18. Thus, applicants submit the specification enables one of ordinary skill in the art to make and use the full scope of the claimed methods for any injury without having to engage in undue experimentation.

3. The specification enables tissue-protection for different conditions

First, it is important to note that the methods of claims 57-58 for the use of a mutein recombinant tissue protective cytokine for protecting against and preventing a tissue injury as well as restoring and rejuvenating tissue and tissue function in a mammal are effective for protecting against and preventing a tissue injury as well as restoring and rejuvenating tissue and tissue function in a mammal *regardless of the cause of the injury to the tissue.*

Second, Applicants submit herewith a copy of the Declaration of Michael L. Brines of February 26, 2003 ("Brines Declaration") that had been submitted in connection with U.S. Application No.: 09/716,960. In particular, the Examiner's attention is directed to ¶17 in the Brines Declaration, where Dr. Brines discusses the ability of EPO to protect against and alleviate the symptoms of neurodegenerative diseases irrespective of the primary cause of the individual neurodegenerative disease. Similarly, other conditions, irrespective of their primary cause, result ultimately in a loss of viability of individual cells. Because the effects of different conditions can be alike on a cellular level, EPO's beneficial effect in protecting, maintaining, and enhancing the viability of cells is beneficial irrespective of the underlying condition.

Finally, it is important to note that the Examiner has provided no reason to doubt that the teachings relied on for enabling support will not work across the full scope of the claims. In particular, the Examiner has not cited any reason to expect that the cause of the tissue injury would alter the effectiveness of mutein recombinant tissue protective cytokine in protecting against and preventing a tissue injury as well as restoring and rejuvenating tissue and tissue function in a mammal. According to applicable case law, the Patent and

Trademark Office bears the initial burden of establishing a *prima facie* case of non-enablement. *In re Marzocchi*, 169 USPQ 367, 369 (C.C.P.A. 1971); M.P.E.P. § 2164.02. A patent applicant's specification which contains a teaching of how to make and use the invention must be taken as enabling unless there is reason to doubt the objective truth of the teachings which must be relied on for enabling support. *Id.* In this case, the Examiner has provided no such reason for doubt.

The Examiner contends that Applicants fail to show that any tissue protective cytokine completely prevents injury. (Office Action, p. 14, l. 18 – p. 15, l. 2). Applicants point out that prevention also includes reduced tissue injury. Moreover, although "prevention" also includes total prevention, there is no legal requirement that every embodiment within the scope of the claim be demonstrated by working examples. In light of these Arguments, Applicants maintain that the claimed invention is enabled, and Applicants respectfully request that the rejections under 35 U.S.C. §112, first paragraph, enablement, be withdrawn.

4. No undue experimentation is required to make and use *any* mutein recombinant tissue protective cytokine (claims 54-58)

Examiner contends the specification is not enabling for any mutein recombinant tissue protective cytokine. Applicants disagree.

First, Applicants note that in their response to the Restriction Requirement dated December 20, 2006, SEQ ID NO: 62 was elected as the species of tissue protective cytokine. (*See* p. 17, ll. 6-8). The Examiner has acknowledged Applicants election and has indicated that SEQ ID NO: 62 is under examination in the instant Office Action. (*See* page 3, para. 6). Nevertheless, as set forth below, the instant specification provides sufficient guidance to one of ordinary skill in the art to make and use the mutein recombinant tissue protective cytokines of the present invention. *See e.g.,* Example 3.

The mutein recombinant tissue protective cytokines that can be used with the claimed methods can be generated and identified by the skilled artisan without undue experimentation. First, the nucleotide and amino acid sequence of wild-type EPO was known. EPO with a mutant amino acid sequence could be generated by the skilled artisan using merely routine recombinant DNA technology, which was readily available at the time the application was filed. These mutant forms of EPO could then be tested for (1) the lack of at least one activity selected from increasing hematocrit, vasoactive action, hyperactivating

platelets, pro-coagulant activity and increasing production of thrombocytes; and (2) the presence of at least one responsive cellular protective activity selected from the group consisting of protecting, maintaining, enhancing or restoring the function or viability of a responsive mammalian cell, tissue or organ. Neither the generation of these mutant forms of EPO nor the tests of these mutant forms would require a level of ingenuity beyond what is expected from one of ordinary skill in the field. *See Fields*.

(a) Generation of Mutant EPO is Not Undue

Examples of such modifications to the EPO sequence are described in the specification, *e.g.*, at p. 46, ll. 13-24, 47, ll. 6-10, and in Example 3 at pp. 89-102. For example, specific modifications to the EPO molecule include, *e.g.*, site-directed mutagenesis and PCR-mediated mutagenesis. Numerous examples of specific nucleic acid sequences of the EPO molecule that were modified by routine methods to obtain illustrative mutein EPOs are described, *e.g.*, in Example 3. Additional methods for obtaining the required modifications were also well-known in the art, including chemical mutagenesis, in vitro site-directed mutagenesis, oligonucleotide-directed mutagenesis, PCR-based overlap extension, PCR-based megaprimer mutagenesis. *See* p. 38, ll. 24-34. Furthermore, throughout the specification are provided examples of specific resulting mutein recombinant EPO molecules which may be used in the claimed invention. For example, particular mutein recombinant EPO molecules are provided at, *e.g.*, pages 32-35 and 47-49 of the specification, and, *e.g.*, in Example 3 at page 89-102.

(b) Testing for Lack of Erythropoietic Activity is Not Undue

Furthermore, the specification provides ample guidance of testing for the lack of erythropoietic activity. Specifically, in Example 6.17, beginning on page 126, Applicants discuss in detail the EPO bio-assay UT-7 cell proliferation. This assay measures the proliferation response which is a quantitative measure of and correlates with the capacity of different forms of EPO to stimulate the classical EPO receptor.

Using the assay disclosed in the specification, the skilled artisan, at the time the application was filed, could have determined which mutein recombinant tissue protective cytokine lacked erythropoietic activity and could be used with the claimed methods. Performance of this assay was routine and did not require more than ordinary skill. Simply because the outcome of a specific assay for each recombinant mutein tissue protective

cytokine may not be known in advance does not make the claimed methods non-enabled because unpredictability of the result of an experiment is not a basis to conclude that the amount of experimentation is undue.

In addition, the specification discloses at p. 62, line 26 to p. 63, line 8, that the TF-1 assay can be used to determine the erythropoietic activity of a compound.

(c) Testing for Tissue-Protection is Not Undue

Furthermore, the specification provides ample guidance for the identification of recombinant forms of tissue protective cytokines that are suitable for the claimed methods. *See*, inter alia, Example 6.3 and Example 6.6. As described above, numerous assays are provided within the specification for identifying mutein recombinant forms of tissue protective cytokines that are suitable for the claimed methods of protecting, maintaining, enhancing or restoring the function of tissue.

Illustrative assays to test the tissue-protective activity of a tissue protective cytokine are provided at p. 63, *ll.* 12-16, of the specification as originally filed. For example, the P-19 and PC-12 assays are cell-culture based assays that require merely routine work to test the tissue-protection of a given EPO.

Using the assays disclosed in the specification, and described above, the skilled artisan, at the time the application was filed, could have determined which mutein recombinant tissue protective cytokine could be used with the claimed methods. Performance of these assays was routine and did not require more than ordinary skill. Simply because the outcome of a specific assay for each recombinant mutein tissue protective cytokine may not be known in advance does not make the claimed methods non-enabled because unpredictability of the result of an experiment is not a basis to conclude that the amount of experimentation is undue. *See Neuberger.*

Thus, Applicants respectfully submit that they have cited to sufficient evidence and the specification shows numerous examples to teach one of ordinary skill in the art to make and use the claimed methods of the present invention, and therefore, request withdrawal of these rejections.

IV. THE CLAIM REJECTIONS UNDER 35 U.S.C. § 112, FIRST PARAGRAPH, WRITTEN DESCRIPTION, SHOULD BE WITHDRAWN

Claims 54-58 have been rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. As discussed in detail below, Applicants disagree with the Examiner's contentions and that the claims should be allowed.

A. The Legal Standard

The test for sufficiency of written description is whether the disclosure of the application "reasonably conveys to the artisan that the inventor had possession" of the claimed subject matter. *In re Kaslow*, 707 F.2d 1366, 1375, 217 U.S.P.Q. (BNA) 1089, 1096 (Fed. Cir. 1983); *accord Vas Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563; *see also, Ralston Purina Co. v. Far Mar Co, Inc.*, 772 F.2d 1570, 1575, 227 U.S.P.Q. (BNA) 177, 179 (Fed. Cir. 1985). The Court of Appeals for the Federal Circuit has repeatedly considered the written description requirement and consistently found that exacting detail is not necessary to meet the requirement:

> If a person of ordinary skill in the art would have understood the inventor to have been in possession of the claimed invention at the time of filing, even if [not] every nuance of the claims is explicitly described in the specification, the adequate written description requirement is met. *In re Alton*, 76 F.3d 1168, 37 USPQ2d 1578 (Fed. Cir. 1996).

The criteria for determining sufficiency of written description set forth in Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112 ¶ 1, "Written Description Requirement" ("the Guidelines") (published in the January 5, 2001 Federal Register at Volume 66, Number 4, p. 1099-1111), specifies that:

> The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice (see (1)(a) above), reduction to drawings (see (1) (b) above), or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus (see (1)(c), above). *Id.* at p. 1106, column 3, l. 13-29.

Where the specification discloses any relevant identifying characteristics, *i.e.*, physical, chemical and/or functional characteristics sufficient to allow a skilled artisan to recognize the applicant was in possession of the claimed invention, a rejection for lack of written description under Section 112, first paragraph, is misplaced. *Id.*

Furthermore, in accordance with the Guidelines, what is conventional or well known to one of skill in the art need not be disclosed in detail (*Id.* at p. 1105, column 3, ll. 39-41), and, where the level of knowledge and skill in the art is high, a written description question should not be raised. *Id.* at p. 1106, column 1, ll. 34-36. See also *Capon v. Eshhar*, 418 F.3d 1349, at 1357 (Fed. Cir. 2005).

B. Claims 54-58 Are Described by the Instant Specification

The Examiner contends that the instant specification fails to provide support for any mutein recombinant tissue protective cytokine. Applicants disagree.

Applicants note that in their response to the Restriction Requirement dated December 20, 2006, SEQ ID NO: 62 was elected as the species of tissue protective cytokine. (*See* p. 17, ll. 6-8). The Examiner has acknowledged Applicants election and has indicated that SEQ ID NO: 62 is under examination in the instant Office Action. (*See* page 3, para. 6). Nevertheless, as set forth below, the instant specification provides sufficient disclosure to support any mutein recombinant tissue protective cytokines of the present invention. *See e.g.*, Example 3.

The present specification provides sufficient written description by virtue of (1) numerous working examples and (2) a disclosed correlation between structure and function.

(1) Working Examples

Examples of specific nucleic acid sequences that encode EPO muteins which lack erythropoietic activity compared to EPO, *see* Example 17, and are tissue protective are described in the instant specification. This is shown in Example 3 (S100E), Example 11 (S100E), Example 14 (R130E and R150E), Example 15 (S100E), Example 16 (S100E), and Example 18 (R103E, R150E, S100E).

Furthermore, throughout the specification are provided prophetic examples of specific resulting mutein recombinant EPO molecules which may be used in the claimed invention. For example, particular mutein recombinant EPO molecules are provided at, *e.g.*, pages 32-35 and 47-49 of the specification.

From the known nucleotide sequence and amino sequence of EPO in combination with the disclosed mutations and changes to the EPO molecule, the skilled artisan can readily deduce the structure of the mutein EPOs.

(2) Disclosed Correlation between Structure and Function

The instant specification teaches to one of ordinary skill in the art that certain regions of the amino acid structure of recombinant human EPO correlate to a specific function or lack thereof. *See* page 4, line 20 to page 5, line 2. Specifically, the regions TKVNFYAW (amino acids 44-51 of native human EPO) and SGLRSLTTL (amino acids 100-108 of native human EPO) are involved with the erythropoietin activity of the molecule. *Id.* Mutations in one or more amino acids of either of these regions yields a mutein recombinant human EPO having reduced erythropoietic activity compared to recombinant human EPO. *Id.*

The written description requirement is met where, as here, the specification discloses numerous working examples and a disclosed correlation between structure and function allowing a skilled artisan to recognize the applicant was in possession of the claimed invention at the time of filing. Thus, the rejection of claims 54-58 under 35 U.S.C. § 112, first paragraph, written description, is improper and should be withdrawn.

V. THE CLAIM REJECTIONS UNDER 35 U.S.C. § 112, SECOND PARAGRAPH, INDEFINITENESS, SHOULD BE WITHDRAWN

Claim 55 has been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner contends that the claim is indefinite because the recitation "wherein the protection does not effect bone marrow" is unclear how the tissue protective cytokine could effect bone marrow if it is being used on cell, tissue, or organ that is isolated from a mammalian body, *i.e.*, directed to *ex vivo* exposure of the cell, tissue or organ to the cytokine. Further, the Examiner contends that, if the cell, tissue, or organ to be protected is isolated from the body, there would be no interaction with bone marrow.

As discussed in detail below, Applicants have amended claim 55 to expedite prosecution of the application.

A. The Legal Standard

"The essential inquiry pertaining to this requirement is whether the claims set out and circumscribe a particular subject matter with a reasonable degree of clarity and particularity. Definiteness of claim language must be analyzed, not in a vacuum, but in light of:

(A) The content of the particular application disclosure;

(B) The teachings of the prior art; and

(C) The claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made." M.P.E.P. § 2173.02.

"The primary purpose of this requirement of definiteness of claim language is to ensure that the scope of the claims is clear so the public is informed of the boundaries of what constitutes infringement of the patent." M.P.E.P. § 2173.

B. Claim 55 Complies With The Definiteness Requirement

Applicants have amended claim 55 to recite "wherein the mutein recombinant tissue protective cytokine does not affect bone marrow." This amendment makes clear to one of ordinary skill in the art what is meant by the claim. In particular, the correction of this typographical error clarifies that the it is the ability of the cytokine that is being used in the method of claim 54 that is further defined in claim 55.

First, the specification defines that effects on bone marrow entail increased hematocrit (erythropoiesis), vasoactive action (vasoconstriciton/vasodialation), hyperactivation of platelets, increased production of thrombocytes, and pro-coagulant activities. See, p. 4, lines 12-15.

Second, the specification provides assays for determining whether or not a given EPO has any of these activities. Specifically, Applicants provide an example of the TF-1 assay. See, p. 62, line 26 to p. 63, line 8. The specification further provides the UT7 assay to test erythropoietic activity. See, Example 6.17, beginning on page 126.

Furthermore, in response to the Examiner's concern that the term "effect" is unclear, Applicants direct the Examiner to p. 63, line 2, of the specification. The "effect" on bone marrow refers to whether the TF-1 cells in the TF-1 assay proliferate. Specifically, the specification recites:

> If the cells proliferate, the recombinant tissue protective cytokine may be erythropoietic. The in vivo effect of the compound should then be tested on an in vivo assay monitoring the increase of hematocrit due to the recombinant tissue protective cytokine. A negative result--non proliferation of cells in the TF-1 in vitro assay and/or no increase in hematocrit within the in vivo assay--means that the recombinant tissue protective cytokine is nonerythropoietic.

Thus, Applicants submit that one of ordinary skill in the art reading claim 55 would know exactly its metes and bounds, *including* whether the protection does not effect bone marrow.

For the reasons set forth above, Applicants request the rejection of claim 55 under 35 U.S.C. § 112, second paragraph, definiteness, is improper and should be withdrawn.

VI. THE CLAIM REJECTIONS UNDER 35 U.S.C. § 112, SECOND PARAGRAPH, AS BEING INCOMPLETE FOR OMITTING ESSENTIAL STEPS, SHOULD BE WITHDRAWN

Claims 54-58 have been rejected under 35 U.S.C. § 112, second paragraph, as being incomplete for omitting essential steps. Specifically, the Examiner contends that the omitted step is a conclusion step indicating that exposure to or administration of the tissue protective cytokine resulted in protection, maintenance or enhancement of viability (as in claims 54-56) or protection against tissue injury, etc. (as in claims 57-58).

Solely to expedite the prosecution of the present application, Applicants have amended the claims 54, 56, and 57 to recite a conclusion step. In view of this amendment, the rejections of claim 54-58 under 35 U.S.C. § 112, second paragraph, as being incomplete for omitting essential steps are moot.

VII. THE CLAIM REJECTIONS UNDER 35 U.S.C. § 102(b) OVER WO 94/24160 to BOISSEL ET AL. SHOULD BE WITHDRAWN

Claims 54-56 have been rejected under 35 U.S.C. § 102(b), as being anticipated by WO 94/24160 to Boissel et al., published October 27, 1994. As discussed in detail below, Applicants disagree with the Examiner's contentions that claims 54-56 are anticipated.

Claims 57-58 have been rejected under 35 U.S.C. § 102(b), as being anticipated by U.S. Patent No. 6,153,407 to Sytkowski et al, issued November 28, 2000. As discussed in detail below, Applicants disagree with the Examiner's contentions that claims 57-58 are anticipated and that the claims should be allowed.

A. The Legal Standard

The standard for an anticipatory reference is set forth in *Verdegaal Bros. v. Union Oil Co. of California,* 814 F.2d 628, 631 (Fed. Cir. 1987): "[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described in a single prior art reference." *See also Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236 (Fed. Cir. 1989)holding that "[t]he identical invention must be shown in as complete detail as is contained in the . . . claim").

To establish anticipation by inherency of a result or characteristic, it is not enough that certain result or characteristic may occur or be present in the prior art. *In re Rijckaert*, 9 F.3d 1531, 1534 (Fed. Cir. 1993). "In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." *Ex parte Levy*; 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990).

B. BOISSEL DOES NOT ANTICIPATE THE PRESENT INVENTION

Claims 54-56 have been rejected under 35 U.S.C. § 102(b), as being anticipated by WO 94/24160 to Boissel et al., published October 27, 1994. ("Boissel").

Applicants disagree that Boissel anticipates claims 54-56. The Examiner asserts:

> "Boissel teaches assessment of the mutein EPO proteins using bioassays such as Example II on p. 43, and discloses a bioassay using EPO-dependent mouse and human cell lines to evaluate the biological activity of particular mutein recombinant molecules. *Exposure of the cells to the mutein recombinant EPO would be expected to inherently result in their protection, maintenance or enhance their viability. (emphasis added).*
>
> *See* Office Action at page 22.

Respectfully, the Examiner has failed to provide a *prima facie* case of inherency by failing to establish that the alleged inherent result *necessarily* flows from the discussion in Boissel. The courts and the MPEP require more than a mere expectation to establish inherency. *See Akamai Technologies, Inc. v. Cable & Wireless Internet Services, Inc.*, 344 F.3d 1186, 1192 (Fed Cir. 2003) ("A claim limitation is inherent in the prior art if it is necessarily present in the prior art, not merely probably or possibly present."); MPEP § 2112 (IV)("[I]n relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." *Ex parte Levy,* 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990) (emphasis in original)). Nothing in Boissel indicates that pharmaceutical compositions comprising Boissel's erythropoietin muteins will *necessarily* protect, maintain or enhance the viability of a cell, tissue or organ isolated from a mammalian body. The bioassay in Boissel identified by the Examiner does not measure or establish the ability of Boissel's muteins to *necessarily* protect, maintain or

enhance the viability of a cell, tissue or organ isolated from a mammalian body and instead measures dose-ranging bioactivity of EPO muteins.

Furthermore, Boissel is specifically concerned with enhancing the ability to stimulate red blood cell production of EPO by creating EPO muteins rather than the method detailed in Applicant's presently claimed method. In view of this difference between Boissel's method and Applicants' claimed method, the Examiner has failed to establish that the muteins of Boissel will *necessarily* protect, maintain or enhance the viability of a cell, tissue or organ isolated from a mammalian body. Accordingly claims 54-56 are not anticipated by Boissel and Applicants respectfully request reconsideration and withdrawal of this rejection.

C. SYTKOWSKI DOES NOT ANTICIPATE THE PRESENT INVENTION

Claims 57-58 have been rejected under 35 U.S.C. § 102(b), as being anticipated by U.S. Patent No. 6,153,407 to Sytkowski et al, issued November 28, 2000.

Similar to the rejection in view of Boissel, the Examiner has failed to establish a *prima facie* case of anticipation of claims 57-58 in view of Sytkowski. Sytkowski discusses use of modified erythropoietin with decreased biological activity in decreasing growth and differentiation of red blood cell precursors in certain leukemias and polycythemias. *See* Column 4, lines 38-42. In contrast to the presently claimed invention, however, Sytkowski does not teach how to obtain tissue-protective EPO proteins. Although some of the EPO proteins disclosed by Sytkowski may or may not be tissue-protective, Sytkowski fails to teach how to obtain EPO proteins that are tissue-protective but lack erythropoietic function. In fact, Sytkowski is completely silent as to the existence of such forms of EPO.

The Examiner asserts that:

> Further, Sytkowski teaches that such modified recombinant mutant erythropoietin has decreased biological activity relative to wild type erythropoietin protein, such as the ability to regulate growth and differentiation of red blood cell progenitor cells. . ., which would anticipate the instantly claimed tissue protective cytokine 'that lacks at least one at least one activity selected from the group consisting of increasing hematocrit, vasoactive action, hyperactivating platelets, pro-coagulant activity and increasing production of thrombocytes.'

See Office Action at page 23-24.

Applicants respectfully disagree. The modified EPO proteins of Sytkowski are indicated as having decreased biological activity, but none are identified as still protecting against and preventing a tissue injury as well as restoring and rejuvenating tissue and tissue function in a mammal. In fact, Sytkowski is silent with respect to "protecting against and preventing a tissue injury as well as restoring and rejuvenating tissue and tissue function in a mammal."

Additionally, contrary to the Examiner's assertion that because SEQ ID NO: 62 has a Ser-Glu substitution at residue 100 and that Sytkowski teaches modifying EPO at any of residues 99-110, Sytkowski anticipates it, there is no specific disclosure within Sytkowski of a substitution at residue 100 of this nature. In fact, Sytkowski discusses a substitution of Ser-Ala at residue 100 and specifically indicates that such a substitution was found to have an increase, though not a statistically significant increase, in activity when compared to wild type EPO. *See* Sytkowski at col. 11, line 66 to col. 12, line 24. Accordingly, Sytkowski suggests that substitution at residue 100 would have an increase in the biological activity of EPO and not create a lack of any of the specific activities in the claim. This fact, when coupled with the additional fact that that Domain 1 of Sytkowski includes 12 amino acids each of which may be substituted by numerous amino acids, shows that Applicant's claimed invention could not be "at once envisaged" by one of ordinary skill in the art based on this disclosure as required by the MPEP. *See* MPEP § 2131.02

As mentioned above, the standard for an anticipatory reference is set forth in *Verdegaal Bros. v. Union Oil Co. of California,* 814 F.2d 628, 631 (Fed. Cir. 1987): "[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described in a single prior art reference." *See also Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236 (Fed. Cir. 1989) holding that "[t]he identical invention must be shown in as complete detail as is contained in the . . . claim"). Sytkowski fails to teach these two elements of the claims.

The Examiner continues with the assertion that:

> Sytkowski teaches that such modified EPO proteins, with altered regulating ability can be used for therapeutic purposes, and that pharmaceutical compositions comprising an effective amount of the modified human recombinant EPO may be used in these methods (see column 4, lines 34-36 and 61-64). Sytkowski discloses administration to "patients" and "individuals" (see, for example, columns 19-21), which are generally accepted to mean humans, and thus would address the limitation of mammal

in the instant claims. Accordingly, administration of an effective amount of the modified recombinant EPO protein with the decreased erythropoietin activity to an individual would inherently result in the claimed protection of tissue injury and/or restoration of the tissue function, etc., regardless of the cause of the tissue injury. Accordingly, the US patent to Sytkowski et al. anticipates instant claims 57-58.

Respectfully, Applicants disagree. As indicated above, Sytkowski fails to teach a method for the protecting against and preventing a tissue injury as well as restoring and rejuvenating tissue and tissue function in a mammal comprising exposing said tissue to a recombinant tissue protective cytokine of any one of claims 1, 2, 3, 4, 5, or 6, that lacks at least one activity selected from the group consisting of increasing hematocrit, vasoactive action, hyperactivating platelets, pro-coagulant activity and increasing production of thrombocytes, wherein the method results in protection against and prevention of a tissue injury as well as restoration and rejuvenation of tissue and tissue function in a mammal..

In addition, similar to Boissel, the Examiner has failed to establish a *prima facie* case that administration of a modified EPO protein according to Sytkowski would necessarily result in protecting against and preventing a tissue injury as well as restoring and rejuvenating tissue and tissue function in a mammal. Specifically, the Examiner has failed to provide a factual and/or technical basis that the alleged inherent result *necessarily* flows from the discussion in Sytkowski. *See Levy.*

Sytkowski discusses a variety of modifications that may be made to EPO protein, some of the changes increase the biological activity of EPO, some decrease the biological activity of EPO, some have no effect, none are specifically related to protecting against and preventing a tissue injury as well as restoring and rejuvenating tissue and tissue function in a mammal. Accordingly, based on

1) the lack of guidance in the art for making functional modifications to EPO protein (*See* Boissel),

2) the difference in use and activity between Sytkowski and the instant claims,

3) the lack of a specific disclosure of the specific recombinant tissue protective cytokine of the current claim in Sytkowski, and

4) the disclosure in Sytkowski that modifications to the EPO protein may increase, decrease or maintain the biological activity of EPO,

the alleged result described by the Examiner is not *necessarily* present as required by the MPEP and the courts to establish inherency. Accordingly, claims 57-58 are not anticipated by Sytkowski and Applicants respectfully request reconsideration and withdrawal of this rejection.

CONCLUSION

Entry of the foregoing amendments and remarks into the record of the above-identified application is respectfully requested. Applicants estimate that the remarks made herein place the pending claims in condition for allowance.

Respectfully submitted,

Date: August 23, 2007

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Enclosures

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